REMARKS

Claims 1-40 and 42-51 are pending. Claim 41 has been previously canceled, without prejudice or disclaimer. Claims 1-40, 42-47, 50 and 51 stand variously rejected under 35 U.S.C. §§ 112, first and second paragraphs. Applicants acknowledge with appreciation that claims 48 and 49 are allowable.

Claim 1 has been amended herein to make explicit what was previously implicit in the term "expression cassette," namely that the polynucleotide sequence is operably linked to a promoter. (See, page 27, lines 9 to 18). Claim 29 has also been amended and is directed to a method for generating an immune response, as described throughout the specification as filed, for example on page 6, lines 16-24. No new matter has been added as a result of these amendments and entry thereof is respectfully requested. The amendments are made to expedite prosecution and are not made for reasons related to patentability.

In view of the following remarks and foregoing amendments, Applicants respectfully request reconsideration of the application.

IDS

Applicants thank Examiner Whiteman for indicating during a telephone conference on August 19, 2003 that he would consider reference A2 (RE 33,653) and that Applicants should disregard the first sentence in the Office Action indicating that this was not considered.

Specification

The specification was objected to for containing embedded hyperlinks. Applicants have removed the hyperlinks by amendment herein, thereby obviating this objection.

35 U.S.C. 112, First Paragraph, Written Description

Claims 1-40 and 42-47 stand rejected as allegedly not described in the specification as filed in such a way as to reasonably convey to the skilled artisan that applicants were in possession of the claimed invention.[1] (Office Action, page 3). In support of this rejection, the Office states:

> The claims recite a structure (polynucleotide encoding an antigenic HIV Pol polypeptide) but do not recite a function for the genus of polynucleotide sequences. In addition, in view of the phrase "HIV Pol polypeptide", the polypeptide has to be identical to one found in an HIV in nature. The

[1] Applicants note that the Office Action indicates that claims 1-40 and 41-47 were rejected. Since claim 41 was previously canceled, Applicants assume this was a typographical error and address the rejection in relation to pending claims 1-40 and 42-47.

> specification does not disclose how to distinguish between natural amino acid sequence and non-natural sequence that is also at least 90% identical. ...
>
> It is not sufficient to support the present claimed invention directed to a genus of a polynucleotide sequence encoding a polypeptide including an immunogenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO:30, 31 or 32. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming a genus of polynucleotide sequences that must posses the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather it is an attempt to preempt the future before it has arrived [citing *Fiers* and *UC Regents v. Eli Lilly*]. ... The skilled artisan cannot envision the detailed structure of a genus of a polynucleotide encoding a polypeptide including an immunogenic HIV Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide comprises a nucleotide sequence having at least 90% sequence identity to the sequence presented in SEQ ID NO:30-32 that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. (Office Action, pages 4-5).

Because it is neither legally nor factually correct to assert that the skilled artisan could not envision the detailed structure of the claimed expression cassettes, Applicants traverse the rejection and supporting remarks.

The fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. *See, e.g., Vas-Cath, Inc.*, 935 F.2d at 1563-64, 19 USPQ2d at 1117. Determining whether the written description requirement is satisfied is a question of fact and the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976). It is not necessary that the application describe the claimed invention *in ipsis verba.* Rather, all that is required is that the specification reasonably convey possession of the invention. *See, e.g., In re Lukach,* 169 USPQ 795, 796 (CCPA 1971). Finally, determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application. *See, e.g., In re Lange,* 209 USPQ 288 (CCPA 1981).

As previously noted, the Patent Office's own guidelines on written description are clear -- the written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing:

> [t]he description need only describe in detail that which is new or not conventional. This is equally true whether the claimed invention is a product or a process. An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that the applicant was in possession of the claimed invention, i.e. complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with known or disclosed correlation between function and structure, or some combination of such characteristics. ...
>
> A "representative number of species" means that the species that are adequately described are representative of the entire genus. ... What constitutes a "representative number" is an inverse function of the skill and knowledge of the art. Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. ... Description of a representative number of species does not require the description be of such specificity that it would provide individual support for each species that the genus embraces. (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099, emphasis added).

Simply put, there is absolutely **no** requirement that Applicants exemplify (or reduce to practice) every sequence falling within the scope of the claims in order to adequately describe the expression cassettes as claimed. Rather, the test is whether the specification contains sufficient disclosure regarding structural and functional characteristics of the claimed sequences to satisfy the written description requirement. In the pending case, the specification as filed more than adequately describes and details both structure and function of the claimed Pol-encoding polynucleotides.

The Scope of the Claims

Because any written description inquiry must begin with claim construction, it is important to note at the outset of this discussion that the claims clearly recite both the structure (sequence) and the function (encode an immunogenic HIV Pol polypeptide) of the recited polynucleotides. Indeed, the claims do not, as asserted in the Office Action, recite only structural characteristics. In addition to exhibiting the claimed sequence identity, the polynucleotides must also encode an immunogenic HIV Pol polypeptide. Therefore, when

properly construed, it is plain that only polynucleotide sequences having the recited structure and function are encompassed by the pending claims.

Applicants also traverse the Office's assertion that the specification requires that the polypeptide encoded by the claimed expression cassettes be "identical" to a naturally occurring Pol polypeptide. (See, Office Action, page 4). As noted above, the pending claims are all directed to synthetic polynucleotide (not amino acid) sequences having the requisite similarity to SEQ ID NO:30-32 and that encode any immunogenic HIV Pol polypeptide. Thus, the polypeptides encoded by the claimed synthetic polynucleotides must encode an immunogenic Pol polypeptide -- in other words, the polypeptide encoded by the claimed molecules must be capable of generating a cellular and/or humoral immune response to HIV Pol. It is clear from the specification as filed that the written description requirement is met with respect the claimed molecules.

The Specification Describes the Claimed Subject Matter

For the reasons of record and those discussed herein, the specification as filed fully describes the claimed subject matter. The specification describes, in detail, how Pol polypeptides are identified, for example by Western blotting, ELISA or the like and how to determine immunogenicity. (See, *e.g.,* Section 2.2.1.3, Examples 2 and 3). Further, sequences of various Pol-encoding polynucleotides (as well as Pol polypeptides themselves) were known at the time of filing and are described, for example, in the Background section and references cited therein. In fact, the specification clearly describes how to determine percent identity as between polynucleotides or polypeptides, for example in the text beginning on line 19 of page 19. Performing such alignments was routine and conventional. Any polynucleotide exhibiting the requisite 90% identity could then be expressed, and the polypeptide product readily tested for immunogenicity, for instance, as described in Examples 4-7 of the specification a filed. (*See, also,* Exhibit B of Donnelly Declaration submitted herewith in which immunogenicity of Pol-encoding constructs is evaluated).

It is axiomatic that the specification need only describe in detail that which is new or not conventional. (See, Guidelines on Written Description, page 275). In the case at hand, a skilled artisan reading the specification would have known that Applicants were in possession of claimed polynucleotides as recited in the claims in view of the specification's extensive disclosure of (1) precise sequences falling in the scope of the claims; (2) conventional, known methods of aligning polynucleotides; (3) conventional, known methods of expressing polynucleotides; and (3) conventional, known methods of testing the expressed polypeptides for immunogenicity. In view of disclosure of the specification and state of the art, it would have

been plain to the skilled artisan that Applicants were in possession of the claimed invention at the time the specification was filed.

Turning now to the Office's assertion that there are insufficient representative species described in the specification to adequately describe the alleged "broad genus" of polynucleotides, Applicants note that a "representative number" does not mean that each and every species falling within the genus must be disclosed. (See, Guidelines on Written Description, reproduced in part above). In the pending case, at least four representative species are described. (SEQ ID NOs:30-32 and 36). For the reasons noted above, it is well within the purview of the skilled artisan, in view of the teachings of the specification, to align polynucleotide sequences and determine those polynucleotides having the requisite similarity to the sequences set forth in the claims. (See, *e.g.*, pages 19-21 and Examples). Accordingly, the representative number of species disclosed in the specification more than adequately conveys to the skilled artisan that Applicants were in possession of the precisely claimed molecules at the time the application was filed.

Declaration Evidence

Submitted herewith is a Declaration pursuant to 37 C.F.R. § 1.132 in which Dr. John Donnelly set forth data and facts relevant to the adequacy of the description found in the specification as filed. As previously noted, such Declaration evidence cannot be ignored. (*see, e.g.*, *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996)). In particular, with regard to written description Dr. Donnelly states:

> 15. It is also my opinion that the specification as filed clearly conveyed to a typical scientist that the inventors had in their possession the invention set forth in the claims (see paragraph 4 above). By "in their possession," I mean that the inventors contemplated the polynucleotides, cells and methods as set forth in the claims and that they had, using the specification and information available to a typical scientist, a practical way of making such molecules and practicing such methods. Thus, I believe that a typical scientist would have understood the specification clearly described all of the various aspects of the claims. I base this belief on the facts set forth herein.
> 16. First, the specification unambiguously and clearly describes at the time the specification was filed, it was widely known how to determine sequence identity to any length polynucleotides. Such methods are described in detail in the specification, for example, on pages 19-21 of the specification. (see, also, paragraph 7 above). Therefore, it is my opinion that the specification describes any sequence exhibiting 90% sequence identity to SEQ ID NOs:30-32.
> 17. Second, at the time the specification was filed, it would have been clear to a typical scientist that the inventors' specification fully described and contemplated that the claimed polynucleotides encoded immunogenic Pol

> polypeptides. Methods of testing Pol immunogenicity were well-known at the time of filing and are demonstrated, for example, in Exhibit B. Indeed, our experiments, presented in Exhibit B, indicate that Pol-specific immune responses are generated to the claimed sequences. In sum, based on the disclosure of the specification and the level of knowledge of a typical scientist regarding sequence identity, and testing for immunogenicity, I believe that the specification as filed clearly conveys that the applicants had invented the expression cassettes as set forth in the claims.
>
> 18. In view of the foregoing facts regarding the routine nature of experimentation required to make and use the claimed constructs, the extensive direction provided by the specification, the straightforward nature of the invention, the presence of working examples, the high level of the skilled worker, the sophistication of the art, and the predictability (*e.g.,* of determining sequences identity and immunogenicity) of the art, it is my unequivocal opinion that the specification enabled, in July 2000, a skilled worker to make and use the subject matter of the claims. Similarly, in view of the detailed description in the specification and state of the field at the time of filing, it is my opinion that the specification more than adequately conveys that the inventors had possession of the claimed polynucleotides, expression cassettes, vectors, cells and methods of generating immune responses at the time of filing in July 2000.

Thus, at the time the specification was filed, it was well known how to align polynucleotide sequences to determine percent identity and the specification describes how this would be done. In addition, Dr. Donnelly establishes that the specification teaches how to test any sequence falling within the claimed identity for its ability to express immunogenic HIV Pol polypeptides, including experiments conducted using the protocols and techniques as described in the specification that demonstrate that modified Pol-encoding sequences used in expression cassettes elicit Pol-specific immune responses. (Donnelly Declaration, ¶¶ 12, 17). Thus, Dr. Donnelly provides still further definitive evidence that the claims as pending are fully described by the specification as filed.

The Cases Cited are Not Applicable

Furthermore, the Office's reliance of *Fiers v. Revel* and *Regents of the Univ. Calif. v. Eli Lilly* is misplaced. The written description requirement of § 112 is highly fact dependent and the claims, disclosure and state of the art in *Fiers* and *Eli Lilly* are entirely different from those in the case at hand. Indeed, the issue in *Fiers* or *Eli Lilly* was not whether these specifications disclosed a sufficient number of representative examples, but whether these specifications disclosed any structure at all. In fact, the application in these cases were completely devoid of any representative structural (sequence) examples. In contrast, Applicants' specification, as filed,

and pending claims contain and recite specific sequences (structure) and functional characteristics.

Furthermore, the Federal Circuit's holdings in *Fiers* or *Eli Lilly* in no way necessitate that the claims be limited in scope to those sequences disclosed in SEQ ID Nos. Indeed, in *Fiers v. Revel*, the Federal Circuit indicated that, although disclosure of a method of isolating DNA did not adequately describe the DNA itself, the DNA may be properly defined by one or more of the following parameters: "structure, formula, chemical name or physical properties." Thus, it is possible that DNA can be entirely described by its physical properties, *i.e.* by function. Again, Applicants' disclosure and claims include both structure and physical properties and, accordingly, the cases cited by the Office are not relevant to case at hand.

35 U.S.C. 112, First Paragraph, Enablement

Claims 1-40, 42-47 and 50-51 remain rejected under 35 U.S.C. 112, first paragraph as allegedly not enabled by the specification as filed. It is acknowledged that the specification enables expression cassettes in which the polynucleotide is operably linked to a promoter and methods of generating an immune response by intramuscular injection of a gene delivery vehicle comprising these expression cassettes. (Office Action, page 6). However, it is alleged that the specification does not enable sequences having 90% identity to SEQ ID NO:30-32 or methods of immunization. (Office Action, pages 6-7). In relation to claims allegedly directed to methods of immunization, the Office Action further cites various references (Gurunathan, Nathanson, Azevedo, McCluskie) in support of the position that the immunization is unpredictable. (See, Office Action, pages 7-12). In further support of this rejection, the Office also cites *Genentech v. Novo Nordisk* and *Enzo v. Calgene*. (See, Office Action, page 11).

Applicants traverse the rejection and supporting remarks.

Undue experimentation is not required to practice the claimed invention because the claims are enabled throughout their scope and, in addition, that the references cited by the Examiner do not in any way establish unpredictability. Moreover, declaratory evidence is of record establishing that the disclosure, as filed, enables the claimed invention. When the *Wands* factors are considered, it is clear that the specification as filed fully enables the pending claims throughout their scope.

Promoter

As a threshold matter, Applicants note that the foregoing amendments to the claims now explicitly recite that the claimed Pol encoding sequences of the expression cassette are operably linked to a promoter. Since the Office has agreed that promoter-containing expression cassettes are enabled by the specification as filed, withdrawal of this aspect of the rejection is requested.

Method Claims

The foregoing amendments also obviate the Office's concerns regarding predictability of methods of "immunization." As noted above, the Office acknowledges that the claims are enabled for gene delivery vehicles carrying specific sequences and use of these vehicles to generate immunological responses in mammals when administered intramuscularly. (Office Action, page 8). However, the rejection asserting lack of enablement of methods of immunization has been maintained and several references are cited to allegedly demonstrate the unpredictability of vaccination and immunization. (Office Action, pages 8-18).

None of the pending claims are directed to methods of immunizing or vaccinating. Rather, the relevant claims (claims 29 and claims dependent therefrom) are directed to methods of generating an immune response in a subject, which the Office recognizes are fully enabled by the specification as filed. Thus, because none of the pending claims are directed to methods of "immunization" or "vaccination," the rejection has been obviated and withdrawal thereof is respectfully requested. (See, also, Response filed 18 October 2002).

Moreover, since the references cited in the pending Office Action are all directed to therapies and/or vaccines, they are not relevant to the claims as pending. Thus, the references do nothing to establish that methods of eliciting an immune response to the claimed expression cassettes are not enabled by Applicants' specification.

Modes of Delivery

In addition to allegedly supporting the enablement rejection of methods of "immunization," the references listed above are also cited in the Office Action as allegedly demonstrating the unpredictability of modes of administration other than intramuscular. (Office Action, pages 8-16, citing Gurunathan, Nathanson, Azevedo and McCluskie).

For the reasons of record and reiterated herein, these references are not relevant to the pending claims, none of which is directed to methods of immunizing or vaccinating a subject. Furthermore, these references do not establish that modes of delivery other than intramuscular would be inoperable (would not result in expression of Pol-antigen(s) or in the generation of an immune response). Gurunathan is directed to the use of CD40LT as an adjuvant. Nathanson is directed to vaccines and therapy. For its part, Azevedo is a general review of plasmid-based DNA immunization and clearly teaches that these vectors are known to generate an immune response. (See, "concluding remarks"). Azevedo goes on to state that the particular nature of the immune response generated can be readily tested for each antigen. *Id.* McCluskie is directed entirely to a comparison of routes of administration for vaccination. Indeed, while McCluskie focuses on how various routes of administration produce more or less immunity, a complete

reading of this reference fully supports Applicants claims -- virtually all routes of DNA administration (encoding a variety of heterologous sequences) are able to generate some kind of an immune response in the subject to the polypeptide encoded by the heterologous nucleotide sequence. Thus, the references cited by the Office actually provide evidence that the specification fully enables multiple delivery routes of DNA in order to generate an immune response in a subject.

Still further evidence that the specification as filed, in view of the state of the art at the time of filing, fully enables all routes of delivery has previously been submitted. In this regard, Shiver et al. 1997 *Vaccine* 15:884-887 (Abstract attached as Exhibit D of Rule 132 Declaration submitted herewith) demonstrates that intradermal administration of DNA resulted in immune responses against HIV antigens in rodents and non-primate species. Similarly, Durani et al. 1998 *J. Immunol. Methods* 220:93-103 (Abstract attached as Exhibit C of Dr. Donnelly's Rule 132 Declaration) demonstrates how mucosal (*e.g.,* intranasal and oral) administration of DNA encoding an HIV antigen generates systemic and humoral immune responses. These references demonstrate yet again that the specification as filed fully enables claims encompassing multiple routes of delivery. (See, also ¶ 14 of Donnelly Declaration, submitted herewith).

Percent Identity

The Office has conceded that the specification fully enables the sequences shown in SEQ ID NOs:30-32 and uses of these sequences. Nonetheless, it is still maintained that it would require undue experimentation to determine sequences having 90% identity to those set forth in the claims because there are insufficient representative working examples of sequences exhibiting the requisite percent identity. (Office Action, page 13). This is not a correct application of the law and, moreover, completely refuted by the evidence of record. Applicants are under no legal obligation to teach or exemplify each and every member of a claimed genus. Rather, for a claimed genus, representative examples together with a statement applicable to the genus as whole is sufficient to establish enablement if the skilled artisan would expect the claimed genus could be used in the manner set forth. *See, e.g.,* U.S. Patent and Trademark Office's Training Materials on Enablement, p. 29. The present record is replete with representative examples and statements applicable to the genus as a whole.

Four representative examples of sequences falling within the scope of the claims are provided in the specification. (SEQ ID NOs:30-32 and 36). Further, three of these representative examples are specifically recited in the pending claims, which, as acknowledged by the Office, are separately patentable. In addition to these representative examples, statements applicable to the genus as whole are provided throughout the specification, for example, on page

19 *et seq.* where it is noted how to determine sequences falling within the requisite percent identity.

At the time of filing, determining sequence identity was **utterly routine**. The specification also provides guidance (*e.g.,* Example 1 of the specification) regarding selection and modification of native Pol HIV sequences. Substantial guidance is also given in regards to determining whether a Pol polypeptide is expressed from the claimed expression cassettes and whether this polypeptide is immunogenic, as required by the claims. (See, *e.g.,* Examples 2-7 and Section 2.2.1.3, particularly page 36). Thus, the specification provides ample guidance as to identification, generation, and testing of expression cassettes that can be used in the claimed invention.

The test of enablement is not what is predictable, but what the specification teaches the skilled practitioner in regard to the claimed subject matter. Not every species encompassed by the claims, even in an unpredictable area like the chemical sciences, needs to be disclosed. (*In re Angstadt,* 537 F.2d 498, 504, 190 USPQ 214, 219, CCPA 1976.) The notion that one of ordinary skill in the art must have reasonable assurance of obtaining positive results on every occasion has been emphatically rejected (*Angstadt* at 219). So long as it is clear that some species render the claims operative, the inclusion of some possible inoperative species does not invalidate the claim under paragraph 1, of 35 U.S.C. §112. (*In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, CCPA 1971; *Horton v. Stevens*, 7 USPQ2d 1245, 1247, Fed. Cir. 1988). Further, even evidence of the need for some experimentation does not invalidate a claim on ground of undue experimentation, nor does it fulfill the PTO's burden of proof. (*In re Angstadt* at 504; *In re Morehouse*, 545 F.2d 162, 165, 192 USPQ 29,32, CCPA 1976.)

In view of the working examples and clear teachings of the specification, including actual sequences and teachings regarding how to determine percent identity as between polynucleotides, prepare and administer expression cassettes comprising polynucleotides, express proteins from these expression cassettes and test those proteins for immunogenicity, Applicants submit that a *prima facie* case of non-enablement has not been (and indeed cannot be) established. Whenever the PTO makes such a rejection for failure to teach and/or use the invention, the PTO must explain its reasons for the rejection and support the rejection with (i) acceptable evidence, or (ii) reasoning which contradicts the applicant's claim: the reasoning must be supported by current literature as a whole and the PTO must prove the disclosure requires undue experimentation. *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971). The Examiner has provided no such support for the arguments presented in the current rejection.

The Cases Cited are Not Applicable

The Office also asserts that the facts and holdings of *Genentech v. NovoNordisk* and *Enzo v. Calgene* are applicable to the pending application, allegedly because Applicants provide no more than a "plan or invitation," for example to determine sequences having the requisite percent identity to those set forth in the claims (Office Action, page 14). Neither *Genentech* nor *Enzo* is applicable to the facts of the pending application.

In *Genentech*, the Federal Circuit held that the specification failed to describe the sequence of a specific material to be cleaved, as set forth in their claims. The court also found that continued lack of success in producing the claimed proteins was further evidence of non-enablement. In stark contrast, the specification at issue discloses specific sequences of at least four polynucleotides falling in the scope of the claimed percent identity. Thus, unlike *Genentech*, Applicants are not claiming compositions in which sequence is not disclosed.

Like *Genentech*, the claims at issue in *Enzo* contained no structural limitations whatsoever -- they were defined solely in terms of function. In the pending case, the claims specifically recite both structure and function. As such, there is simply no attempt to "bootstrap a vague statement of a problem into an enabling disclosure," and the cases cited by the Office are not germane to the instant enablement inquiry.

Declaration Evidence

Furthermore, Applicants request consideration of the Rule 132 Declaration, filed herewith. In this Declaration, Dr. John Donnelly establishes that it would have been routine to determine sequences having at least 90% identity to other HIV encoding sequences, given the disclosure of the specification of the parent application.

When Dr. Donnelly analyzed whether the sequences having at least 90% identity to SEQ ID NO:30-32 were enabled, he concluded:

> 5. It is my opinion that, as a technical matter, a skilled worker could have readily made and used the compositions and methods of the pending claims in light of the specification, together with the common general knowledge, tools and methods available in July 2000. I base this opinion on the data and facts set forth below; however, I call attention to the fact that it was considered routine experimentation at the time of filing to determine a sequence having (i) at least 90% sequence identity to SEQ ID NO:30-32 and (ii) encoding an immunogenic Pol polypeptide; to express such polynucleotides in stem cells or their progenitors; to deliver in a variety of ways such polynucleotides to generate an immune response in a subject. In addition, in drawing my conclusions, I have considered the nature of the claims, the quantity of experimentation required to practice the subject matter of the claims, the existence of working examples, the

direction present in the specification, the state of the field at the time the application was filed and the level of skill in the art. ...

7. In July 2000, the quantity of experimentation required to identify sequences exhibiting 90% identity to any given sequence, for example SEQ ID NOs:30-32, was quite low. For example, BLAST software programs were commonly known and readily available on the Internet at this time. This set of programs allows for an easy alignment and determination of percent identity as between any sequences. The skilled worker could have easily used the BLAST or any number of other similar programs to determine the percent identity between sequences (in this case between any given sequence and those presented SEQ ID NOs:30-32). The specification also provides extensive guidance in this regard, for example, on page 19, line 19 to page 21, line 15. Working examples are also provided -- indeed, the specification provides four sequences falling within the scope of the claims (SEQ ID NOs:30-32 and 37). Furthermore, the skilled worker could have readily generated any sequence falling within the scope of the claims using routine methods, for example by utilizing PCR to generate sequences, by introducing point mutations and the like. Thus, it is my opinion that it would have required only routine experimentation to determine sequences falling within the 90% identity, as claimed.

8. In addition, the specification provides significant direction for evaluating whether sequences having 90% identity to SEQ ID NO:30-32 encode an immunogenic Pol polypeptide. Those of us working in the field of gene delivery and immunology are well versed in the various tests for determining immunogenicity, which include computer analysis of sequences, comparison to known immunogenic sequences as well as functional tests (*e.g.*, ELISAs, CTL assays and others described in the Examples of the specification). Pol antigens or antibodies recognizing Pol antigens had long been used to test for Pol-stimulated immune responses (*e.g.*, n immunoassays). ELISPOT assays for testing cellular immunity were also well known at the time of filing.

9. Furthermore, the state of the art in July 2000 was quite sophisticated with regard to determining both sequence identity and evaluating immunogenicity. I have described above some of the tools, programs and methods available in the field of recombinant nucleic acid technology in July 2000 and many other examples of homologous nucleic acid molecules that encode immunogenic proteins were also available. Therefore, it is my opinion that, following the guidance of the specification, a scientist could have readily made and used polynucleotide sequences that exhibit at least 90% sequence identity to SEQ ID NO:30-32 and which encode an immunogenic HIV Pol polypeptide.

10. Preparing polynucleotides encoding immunogenic Pol polypeptides in July 2000 was a predictable art. There is no doubt that a skilled worker would have been able to make and use sequences exhibiting 90% identity to SEQ ID NO:30-32 and encoding an immunogenic polypeptide. Even if a rare construct were inoperable for some reason (*e.g.*, it wasn't immunogenic), the skilled worker would have readily modified the construct according to the alternatives available at the time and described in the specification. In other words, to the skilled worker, an inoperable construct would itself be a useful starting material for other

operable constructs. Essentially all molecules that fall within the claims would be useful for making or using defining technical features of the claims, *i.e.*, nucleotide sequences having 90% sequence identity to SEQ ID NO:30-32 and which encoded an immunogenic HIV Pol polypeptide.

11. Similarly, the specification as filed clearly provides ample guidance on how to generate an immune response (humoral and/or cellular) in a subject by administering the claimed sequences. (See, page 7, lines 12 to 23; and Examples 4 and 7). Indeed, in July 2000, it was predictable and routine to evaluate whether an immune response was generated against a polypeptide antigen encoded by an administered polynucleotide, for example using the techniques and tools described above in paragraph 8. Furthermore, the skilled worker would know that generating an immune response does not necessarily mean that the subject will be vaccinated – *i.e.*, protected against HIV infection or derive some therapeutic benefit. The skilled worker would also have known that immune responses are useful for numerous scientific purposes, such as laboratory assays, preparing reagents for virologic and immunologic studies, analyzing immune responses, and preparation of diagnostic kits. Therefore, a skilled worker would have known that the claimed sequences could be used for additional scientific purposes other than seeking protective immunity or a therapeutic benefit. In view of the guidance in the specification, the predictability and state of the art, and high level of the skilled worker, it is plain that it would have been routine to administer a polynucleotide and evaluate whether or not an immune response to the encoded polypeptide was generated in the subject.

12. Experiments conducted in our laboratories demonstrate that expression cassettes that include modified HIV Pol-encoding sequences induce potent Pol-specific immune responses. These experiments are summarized in zur Megede et al. (2002) *J. Virol.* 77(11):6197-6207, attached hereto as Exhibit B. As shown in Exhibit B, we generated modified Pol-encoding sequences from subtype B isolates of HIV using the protocols described in the specification. (*See,* Example 1). Also using techniques set forth in the specification, we inserted these modified Pol-encoding sequences into an expression cassette such that they are operably linked to a promoter. These expression cassettes were administered to living animals and immunogenicity evaluated, using the protocols set forth in the specification. Our results establish that "all of the sequence-modified pol and gagpol plasmids expressed high levels of Pol-specific antigens in a Rev-independent fashion and we were able to induce potent Pol-specific T- and B-cell responses..." (Abstract of Exhibit B). In light of our results, I conclude that modified HIV Pol-encoding sequences can be inserted into expression cassettes such that they are operably linked to a promoter and that these expression cassettes are immunogenic. I also conclude that a variety of sequences exhibiting 90% homology to each other are equally effective. Furthermore, because Pol-encoding sequences can be obtained from any HIV isolate and modified as described in the specification, the results we presented in Exhibit B with regard to subtype B sequences are equally applicable to modified polynucleotides obtained from subtype C isolates, as claimed.

Thus, using specific facts, Dr. Donnelly concludes that practicing the invention of the parent application would not require undue experimentation. Accordingly, Applicants submit that this convincing, factual evidence effectively establishes enablement of the pending claims. (*see, e.g.*, *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir. 1996).

In sum, when the *Wands* factors are considered, it is clear that the record establishes that the specification as filed fully enables the pending claims throughout their scope. Therefore, Applicants submit that this rejection should be withdrawn.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

The Commissioner is hereby authorized to charge any fees under 37 C.F.R. §1.16, §1.17, and §1.21, which may be required by this paper, or to credit any overpayment, to Deposit Account No. 18-1648, referencing Atty. Docket No. 2302-1631.

If there are any remaining issues to be addressed before this case proceeds to issuance, Applicants request that the Examiner contact the undersigned at (650) 493-3400 in order to schedule a personal interview.

Please direct all further written communications regarding this application to:

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Respectfully submitted,

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